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EXAMINER
ANGELL, JON E

ART UNIT	PAPER NUMBER
1635	

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14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/763,682	Applicant(s) BJERKVIG, ROLF	
	Examiner J. Eric Angell	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-22 and 24-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-22 and 24-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Action is in response to the communication filed on 7/29/02 as Paper No. 10. The amendment has been entered. Claim 23 has been cancelled. Claims 12, 19 and 21 have been amended and new claims 29-32 have been added. Rejections that are not reiterated below are withdrawn.

Claim Rejections - 35 USC § 112, second paragraph

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 12-22, and 23-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12, 13, 17, 19, 21, 22, 29, 31 and 32 all recite the phrase "capable of". For instance claim 12 recites the phrase, "a molecule that is capable of interacting with the tumor/host communication pathways" (emphasis added). As another example, claim 22 recites the phrase, "molecule... that is capable of affecting tumor neovascularization" (emphasis added). The recitation "capable of" renders the claims vague and indefinite because it is unclear if the molecule does or does not interact with the tumor/host communication pathway (such as claim 12) and it is unclear if the molecule does or does not affect tumor neovascularization (claim 22).

Claims 14-16, 18, 20, 24-28 and 30 are dependent claims and are therefore rejected for the same reasons.

Claim Rejections - 35 USC § 112, first paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 12-22, 24-28, 30 and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to a composition comprising an encapsulated producer cell capable of producing a genus of any molecule that is an inhibitor of the growth of a CNS tumor that affects neovascularization for the treatment of cancer (i.e. tumor inhibition). This large genus is represented in the specification by only one working example (endostatin). Applicants also disclose three other molecules that may be inhibitors of CNS tumor growth (thrombospondin, angiostatin, and prolactin), however there are no working examples indicating that these molecules can be used in the instant method for treating tumor growth. At most, applicant has express possession of only 4 possible species in a genus which comprises a vast amount different possibilities (considering every possible molecule that could inhibit CNS tumor growth and neovascularization). The written description guidelines note regarding such genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by all members of the genus

in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, there are only four possible elements disclosed, therefore there are no predictable structures or attributes of the entire genus disclosed. There are no particular domains and no structural limitations or requirements which provide guidance on the identification of the molecules which meet these functional limitations (tumor growth inhibition/neovascularization) provided.

> It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, only four species of molecules that may inhibit tumor growth and neovascularization, and only one molecule is describes as a working example (endostatin).

In Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is only the disclosure of four possible anti-tumor/neovascularization molecules, not an adequate number of species to describe the entire genus of anti-tumor/neovascularization molecules encompassed by the claims

Response to Arguments

5. Applicant's arguments have been fully considered but they are not persuasive. Applicants argue that a total of four anti-tumor/neovascularization molecules have been described in the

specification. Specifically, endostatin, angiostatin, thrombospondin, and prolactin. Applicants contend that the description of these four molecules is adequate description for every species encompassed by the claims. However, the disclosure of four molecules does not adequately describe the entire genus of anti-tumor/neovascularization molecules. The specification does not disclose structures/attributes common to the four molecules or any characteristics that would be common to all members of this genus. Therefore, the rejection is maintained.

1. Claims 12-22 and 24-32 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an encapsulated producer cell that expresses an inhibitor of the growth of a CNS tumor and affects neovascularization in rats, does not reasonably provide enablement for an encapsulated producer cell that expresses an inhibitor of the growth of a CNS tumor and affects neovascularization in any animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to a composition comprising a cell "capable" of expressing a molecule inhibiting growth of a CNS tumor, methods for making the composition and methods of using the composition. Therefore, the nature of the Invention encompasses gene therapy as well as cell encapsulation technology.

The breadth of the claims

The breadth of the claims is very broad. For instance the claims encompass a cell that is capable of expressing any molecule that inhibit the growth of a CNS tumor (including ones that affect neovascularization) including angiostatin, endostatin, any apoptotic inducing molecule and functional fragments thereof (just to name a few). There is no limitation in the claim of the type of molecule used to express the therapeutic agent; therefore the claims encompass the use of any vector including viral and non-viral vectors. Furthermore, the treatment claims encompass treating any CNS tumor in any species of animal, including humans.

The unpredictability of the art and the state of the prior art

The current relevant art also considers encapsulated cell technology for treatment of CNS disorders to be unpredictable. For instance, Visted et al. (Neuro-Oncology, July 2001, p. 201-210) recognizes many of the problems related to cell encapsulation technology. Visted et al. teaches that (1) "gene therapy using viral vectors has to date failed to reveal its definitive clinical usefulness" (p. 201, first paragraph); (2) the M component of the alginate used to encapsulate the cells "has immunogenic properties and it may evoke immune reactions when it is present at high concentrations (more than 85%) in the alginate" (see p. 202, under Alginate); (3) "despite promising results reported in several animal experiments, limited graft survival may occur. This

is attributed to host immune reactions against the implant" (see p.204 under Biocompatibility); (4) "microcapsule graft failure is often associated with fibrotic outgrowth of the capsules" (see p. 205, first paragraph); (5) "several cases report that the host produces immunoglobulins against the encapsulated material as well as the secreted recombinant proteins" (see p. 205, under Reaction of the Recipient Against the Encapsulated Cells); (6) "The host's tolerance to xenografts of encapsulated biomaterial also appears to vary between species. Therefore, if specific microcapsules are well tolerated in small animals, testing in large animals is a prerequisite before clinical application." (See p. 205, under Reaction of the Recipient Against the Encapsulated Cells); (7) "only limited information is available on the parenchymal reaction to microcapsules. The alginates, with or without encapsulated producer cells, could theoretically elicit a brisk glial reaction that could abolish any therapeutic benefits" (see p. 205, under Reaction of the Recipient Against the Encapsulated Cells) (8) "There is also limited information available on alginate toxicity/reactivity in the brain in large animal models" (see p. 205, under Reaction of the Recipient Against the Encapsulated Cells); and (9) "Encapsulated cells, however, still have not been applied in any trial that included patients with malignant gliomas" (see p. 207, third paragraph).

Working Examples and Guidance in the Specification

The specification has only one working example of a treatment of a CNS tumor using an encapsulated cell expressing a molecule that affects neovascularization. The disclosed example is the treatment of a rat using an encapsulated cell expressing endostatin. The specification does not provide teachings sufficient to overcome doubts raised in the art with regards to methods of treatment of any animal other than a rat, or the use of any CNS tumor growth inhibitor other than

endostatin. It would essentially be a trial and error process to make and use the diverse species of CNS growth inhibitors encompassed by the claims. It is further not predictable that the claimed treatment method would effectively achieve any therapeutic benefit in any animal other than a rat.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since determination of the efficacy of the encapsulated cell therapy would require, initially, large animal studies before the clinical trials (as mentioned by Visted et al.). After experimentation in the large animal model(s), the efficacy of the treatment would have to be tested in human subjects. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps. Furthermore, all of the different possible growth inhibitors would have to be tested.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability of encapsulated cell technology recognized in the art, the breadth of the claims, the lack of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed method is undue.

Response to Arguments

2. Applicant's arguments have been fully considered but they are not persuasive. Applicants argue that one of ordinary skill in the art would be able to make and use the invention without undue experimentation because of the "abundant direction provided". For instance, applicants contend that undue experimentation would not be required for one of ordinary skill in the art to prepare therapeutic encapsulated cells that would work in any organism susceptible to tumors. Applicants have stated arguments against many of the problems recognized in the art, such as having a G content of above 15% in order to avoid activating the host's immune response.

However, a number of issues that were where set forth in the previous office action regarding the treatment of humans that were not persuasively addressed by the applicants. For instance, as indicated in the previous Office Action (and above) (3) "despite promising results reported in several animal experiments, limited graft survival may occur. This is attributed to host immune reactions against the implant" (see p.204 under Biocompatibility). Applicants respond by arguing that this would not be a problem in the CNS as the immune response of the CNS is mainly cellular, for which the alginate provides protection. However, there is no evidence presented that the limited graft survival would not occur in humans, even though it does not occur in animals. There is no evidence presented that overcomes the unpredictability taught by the cited reference. Also, as previously mentioned, (4) "microcapsule graft failure is often associated with fibrotic outgrowth of the capsules" (see p. 205, first paragraph). Applicants argue that fibrotic outgrowth did not occur in the animal model. It is respectfully pointed out that the method is enabled for the animal model. However, considering the problems recognized in the art regarding the treatment of humans, without evidence to the contrary it is still unpredictable if

the same outcome would occur in humans. In response to (7) "only limited information is available on the parenchymal reaction to microcapsules. The alginates, with or without encapsulated producer cells, could theoretically elicit a brisk glial reaction that could abolish any therapeutic benefits" (see p. 205, under Reaction of the Recipient Against the Encapsulated Cells); applicants contend that this is merely a theoretical problem. However, even theoretical problems indicate unpredictability, without any evidence that a brisk glial reaction would not occur, the issue remains unpredictable. Finally, the primary teaching indicating unpredictability of the method as a treatment for humans: (6) "The host's tolerance to xenografts of encapsulated biomaterial also appears to vary between species. Therefore, if specific microcapsules are well tolerated in small animals, testing in large animals is a prerequisite before clinical application." (See p. 205, under Reaction of the Recipient Against the Encapsulated Cells). Applicants appear to argue that Vista is merely indicating that large animal testing is a prerequisite for human testing, and that it is merely a suggestion on how development should proceed. However, Applicants have not rebutted the argument that the host's tolerance to xenografts of encapsulated biomaterial appears to vary between species. If the host's reaction to the therapeutic compound is not consistent between species, as indicated by the reference, then the example presented in the specification pertaining to rats is not adequate to make the method enabled for human treatment because it is not predictable if the treatment will work in humans.

Claim Rejections - 35 USC § 103

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 12-16, 18-20, 22, 26-29, 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aebischer (WO 97/38707 A1, 1997) in view of Skjak-Braek (U.S. Patent 5,459,054; 1995) and O'Reilly (Cell, Vol. 88:277-285; Jan. 24, 1997).

Aebischer teaches composition comprising a producer cell that expresses a molecule (here FasL) that can be used as a treatment to inhibit CNS tumor growth (see p. 2-3) wherein the cell is encapsulated to protect the cell from the host's immune response (see p. 14).

Aebischer does not teach that the encapsulating matrix is made up of immunoisolating alginate having a G content of above 15%, that the therapeutic molecule affects tumor neovascularization, that the producer cell is present in a bead or a microbead, or the therapeutic molecule produced by the encapsulated cell is endostatin.

Skjak-Braek et al. teaches a composition comprising a producer cell which does not express a molecule that inhibits tumor growth, but is an encapsulated cell wherein the producer cell is encapsulated in a matrix that comprises an immunoisolating alginate having a G content of above 15%, above 50%, 60-80%, and 80-100%, wherein the producer cell is encapsulated in a bead, wherein the alginate is substantially pure of endotoxin, (see abstract; col. 4, lines 44-67; col. 7, lines 15-18; and Example 7). Skjak-Braek et al. also teaches that the encapsulated cells are living cells (col. 4, lines 7-11) which are naturally occurring or genetically engineered prokaryotic or eukaryotic cells (see col. 4, lines 53-57), and that the encapsulated cells "can be implanted or transplanted in vivo into mammals without inducing any substantial immunogenic reaction or fibroblast formation" and can be used "as a drug or biological material delivery system." (See col. 4 lines 44-58).

O'Reilly et al. teaches an inhibitor of angiogenesis and tumor growth known as endostatin (see abstract, fig. 4 and fig. 5). O'Reilly also teaches a recombinant cells that express endostatin (see p. 284, left column).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the therapeutic encapsulated cell taught by Aebischer to such that the cell is encapsulated in the immunoisolating alginate taught by Skjak-Braek and wherein the cell encapsulated cell expresses endostatin as the therapeutic molecule as taught by O'Reilly, with a reasonable expectation of success.

The motivation to combine the references to create claimed invention is provided by Aebischer who teaches that cells expressing therapeutic molecules can be used treat CNS tumors when they are encapsulated in a matrix that protects the cell from the host's immune response.

Response to Arguments

5. Applicant's arguments with respect to claim 12-16, 18-20, 22, 26-29, 31 and 32 have been considered but are moot in view of the new ground(s) of rejection. It is noted that the claims has been amended to indicate that the encapsulated cell express the therapeutic molecule. Aebischer reference has been added to the rejection. Aebischer teaches an encapsulated cell that expresses a therapeutic molecule and that the encapsulated cell can be used to treat CNS, elements that were not covered by Skjak-Braek

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
October 18, 2002

JEFFREY FREDMAN
PRIMARY EXAMINER